CYCLOADDITION APPROACH FOR THE SYNTHESIS OF NOVEL BIOACTIVE COMPOUNDS

SYNOPSIS

OF THE Ph.D. THESIS TO BE SUBMITTED TO THE

MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

MISS THARANGINI K S

DEPARTMENT OF CHEMISTRY
MANGALORE UNIVERSITY
MANGALAGANGOTHRI-574199
KARNATAKA
INDIA

JUNE-2024

SYNOPSIS OF THE Ph.D. THESIS TO BE SUBMITTED TO DEPARTMENT OF CHEMISTRY MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY

TITLE OF THE THESIS: **CYCLOADDITION APPROACH FOR THE SYNTHESIS OF NOVEL BIOACTIVE COMPOUNDS.**

NAME OF THE CANDIDATE: **THARANGINI K S**

NAME OF THE GUIDE: **PROF. BALAKRISHNA KALLURAYA**
RESEARCH GUIDE

DATE OF REGISTRATION: **09/09/2019**

REGISTRATION NUMBER: **MU/EXB/PhD/CR.33/Chem./2022-23/E.23, dated 02.06.2022**

PLACE OF WORK: **DEPARTMENT OF CHEMISTRY**
MANGALORE UNIVERSITY
MANGALAGANGOTHRI-574199
KARNATAKA, INDIA

Heterocyclics are the cyclic organic compounds with at least one atom other than C and H, attached to the ring directly like S, O, N etc. These compounds play a vital role in human life as these compounds have plenty of biological applications. Biological molecules in our body contains many different heterocyclic compounds in their main skeleton. History of heterocyclic chemistry started in 1980s [1] with the discovery of alloxan from uric acid (1818).

Medicinal chemistry plays a vital role as it bridges Chemistry with Medicinal applications and gives a platform to solve the medicinal problems with the help of synthesis of different new organic, inorganic or organometallic compounds. Many biologically active heterocyclic compounds have been synthesized and used for antibiotic, antifungal [2] , anti-inflammatory [3] , antibacterial [4] , antioxidants [5],[6],[7], anticonvulsant [8] , antiallergic [9] , herbicidal activity [10], [11] and anticancer activity [12].

When we examine nature carefully, we could see more of C- Het atom bonds than C-C bonds. 1,2,3 – Triazoles are of immense importance as they are very stable and do not undergo reduction, oxidation or hydrolysis easily. Also, these are stable for metabolic degradation. Triazoles can form hydrogen bonding and hence facilitating easier solubility and bonding of biomolecular moiety. Nitrogen being the component of many important biological molecules like peptides, RNA, DNA, vitamins etc., triazoles have got high biological activity[13]. Traizoles have shown anticancer[14],[15],[16] , antiproliferative[17], antifungal[18] , anti-tuberculosis[19],[20],[21],[22][23], antimicrobial[24],[25] etc properties.

The 1,3-dipolar azide–alkyne cycloaddition (AAC) has been effective for the synthesis of a wide variety of 1,2,3-triazoles [26]. 1,3-Dipolar reaction is a chemical reaction between a 1,3-dipole and a dipolarophile. This reaction is also called as Huisegn reaction as the primary synthetic route and mechanistic view was first given by Rolf Huisegn [27].

Oxadiazoles are a class of heterocyclic aromatic chemical compound of the azole family. There are four isomers of oxadiazole. 1,2,4-Oxadiazole, 1,2,5-xadiazole, and 1,3,4-oxadiazole are all known and appear in a variety of pharmaceutical drugs. 1,2,5-Oxadiazole, and 1,3,4-oxadiazole are known,[28],[29] but the 1,2,3-isomer is unstable and ring-opens to form the diazoketone tautomer.[30] These oxadizole and their derivatives are having high medicinal importance such as anti-inflammatory[31], antimicrobial [32], [33], anticancer [34] , antibacterial [35], [36], pesticidal [37], [38] antihypertensive activities,[39],[40], anticonvulsant activity[41],[42] etc.

Nitrofurans and its derivatives are a class of synthetic heterocycles characterized by the presence of 5-nitro-2-furanyl group. Nitofuran has antimicrobial activity and it was first reported by Stillman et al [43] and Dann et al [44], independently. In 1944, Dodd and Stillman[45] published their findings saying that furans with nitro group in the 5th position possessed antibacterial activity. Nitrofuran dervatives have shown antibacterial[46],[47] , anticanacer[48], schistosomicidal activity[49]

Thiazole derivatives are an important class of compounds with a wide range of medical applications including treatment of HIV and HCV infections[50], antitrichomonal activities [51], fungicidal activities [52], CDK2 inhibitors[53], anti-inflammatory[54], anthelmintic[55], antimicrobial, antifungal[56], antitubercular[57] and antioxidant activities[58].

Schiff bases, named after Hugo Schiff [59] are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known asimine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C,O) has been replaced by an imine or azomethine group. Schiff bases are known to have antimalarial [60], antibacterial [61], antifungal [62], antiviral [63], [64] etc properties.

Owing to the application of aforementioned heterocycles, it was envisioned to synthesise few of the above class of heterocyclic compounds and investigate their biological activity.

The thesis entitled "**Cycloaddition Approach for the Synthesis of Novel Bioactive Compounds**" has been divided into 5 chapters as follows.

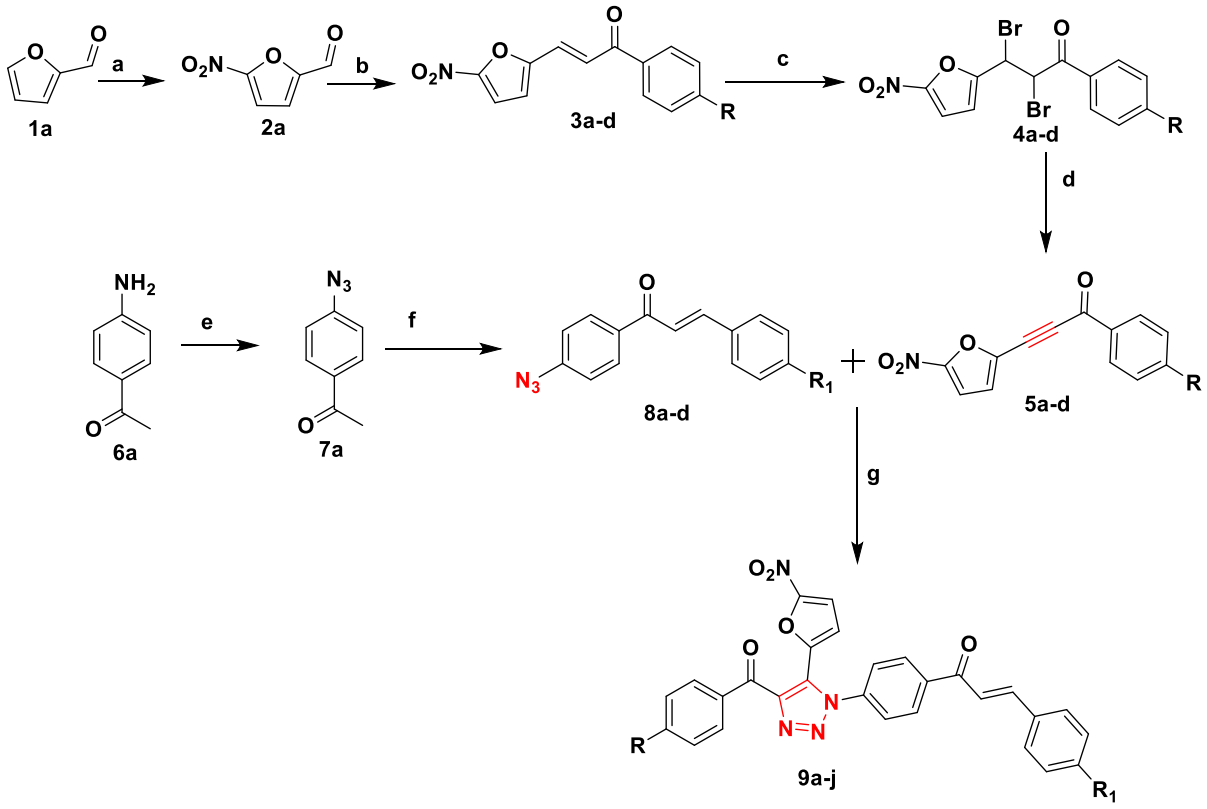
Chapter 1: A brief review on chemistry of 1,3-dipolar cycloaddition reaction and biological activity of few nitrogen, oxygen and sulfur containing heterocycles

This is an introductory chapter which deals with literature review of 1,3-dipolar cycloaddition reaction and biological activity of few nitrogen, oxygen and sulfur containing heterocyclic compounds.

Chapter 2: Synthesis and biological evalution of 1,2,3-triazole derivatives containing 5-nitro furan moiety.

The synthetic strategy for the target molecule (**9a-j**) is shown in **Scheme 1**. Furfural was nitrated which was then converted to various chalcones (**3a-d**) through Claisen-Schmidt condensation reaction. Chalcones were then brominated in the presence of acetic acid and later

debrominated in dry benzene medium employing triethylamine as base to yield acetylenic ketones (**5a-d**). Terminal azido chalcones (**8a-d**) were synthesised by diazotizing 4-amino acetophenone which was later subjected to Claisen-Schmidt condensation with different substituted aromatic aldehydes. Intermediates **5a-d** and **8a-d** were taken in tert-butanol and water (2:1) medium with $CuSO_4.5H_2O$ and sodium ascorbate to yield final compounds namely **1-(4-(4-benzoyl-5-(5-nitrofuran-2-yl)-1H-1,2,3-triazol-1-yl)phenyl)-3-phenylprop-2-en-1-one** derivatives (**9a-j**). Synthesised compounds were confirmed by elemental analysis, FT IR, LC MS, ^{1}H NMR and ^{13}C NMR and were tested for their biological activity.



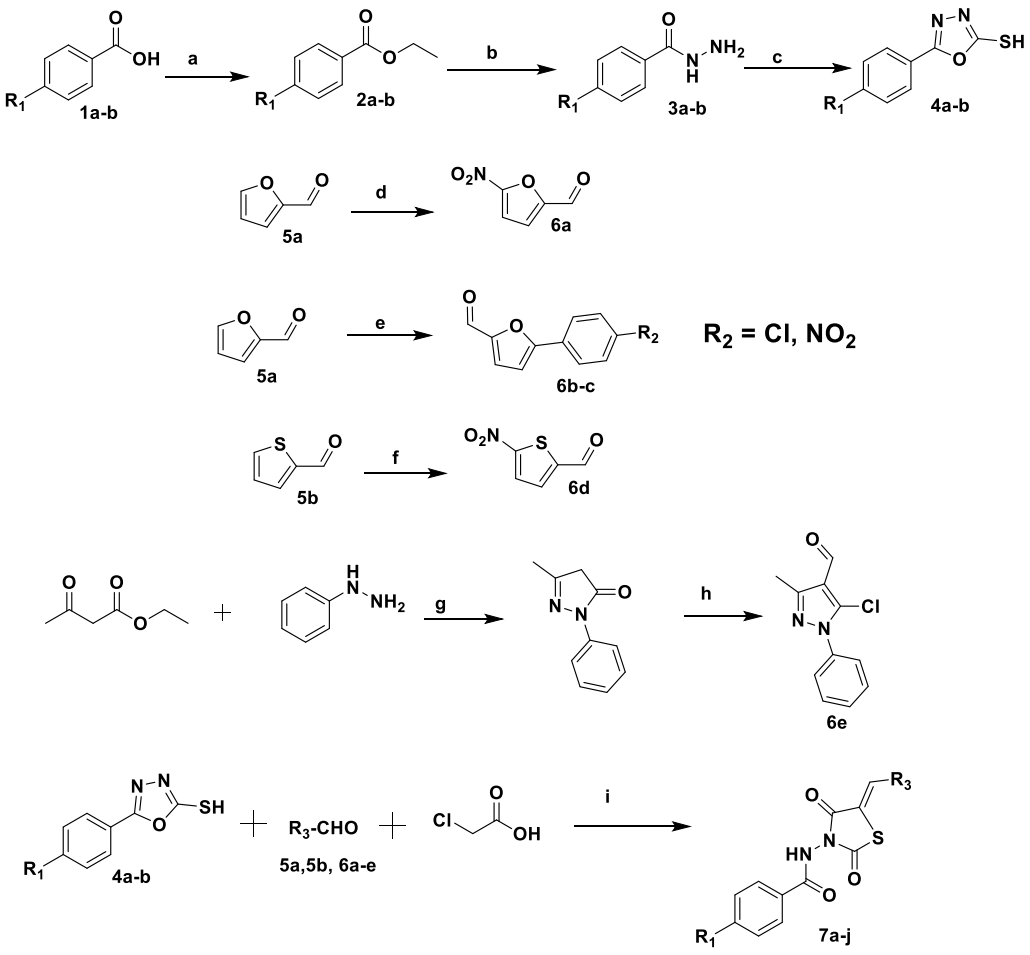
Where R and R_1 are Me, OMe, 3,4-$(OMe)_2$, Cl

Scheme 1: Synthetic strategy for 1,2,3-triazole derivatives.

Reagents and Conditions: a) acetic anhydride, Conc. HNO_3-H_2SO_4, CH_3COONa, Pyridine 0-rt, 16h . b) substituted acetophenones, Conc. H_2SO_4 , acetic acid, rt, 6-7h. c) Br_2 in acetic acid, rt, 18h. d) dry benzene, trimethylamine, rt, 6-7h. e) Conc. HCl, H_2O, $NaNO_2$, NaN_3, 0-rt, 16h. f) substituted aromatic aldehydes, Conc. H_2SO_4 , acetic acid, rt, 6-7h. g) t-BuOH- H_2O (2:1), $CuSO_4.5H_2O$, sodium ascorbate, reflux, 6-7h.

Chapter 3: Synthesis and biological evaluation of dioxothiazolidin containing benzamide

Synthetic strategy for the target compounds **7a-j** is shown in **Scheme 2**. Substituted aromatic acids (**1a-b**) were esterified (**2a-b**) and later converted to their corresponding hydrazides (**3a-b**). The hydrazides (**3a-b**) were converted to their corresponding oxadiazole thione derivatives (**4a-b**) in DMF medium with KOH as base. Various heterocyclic aldehydes were synthesised as follows; Furfuarl (**5a**) was nitrated to obtain **6a**. Diazotisation of appropriate anilines followed by coupling with furfural gave aldehydes **6b-c**. Thiophene aldehyde (**5b**) was nitrated to get **6d**. For the synthesis of intermediate **6e**, phenyl hydrazine and ethylacetoacetate were heated in water bath for 2 hours and later converted to pyrazole aldehyde by Vilsmeier–Haack reaction. Target compounds **N-(5-methylene-2,4-dioxothiazolidin-3-yl)benzamide** derivatives (**7a-j**) were synthesised by refluxing substituted oxadizole thiones (**4a-b**) with various synthesised aldehydes (**5a-b, 6a-e**) in the presence of monochloroacetic acid, acetic anhydride and sodium acetate in glacial acetic acid medium. Synthesised compounds were confirmed by elemental analysis, FT IR, LC MS, ^{1}H NMR and ^{13}C NMR and were tested for their biological activity.



Where R_1 = -Me, -OMe

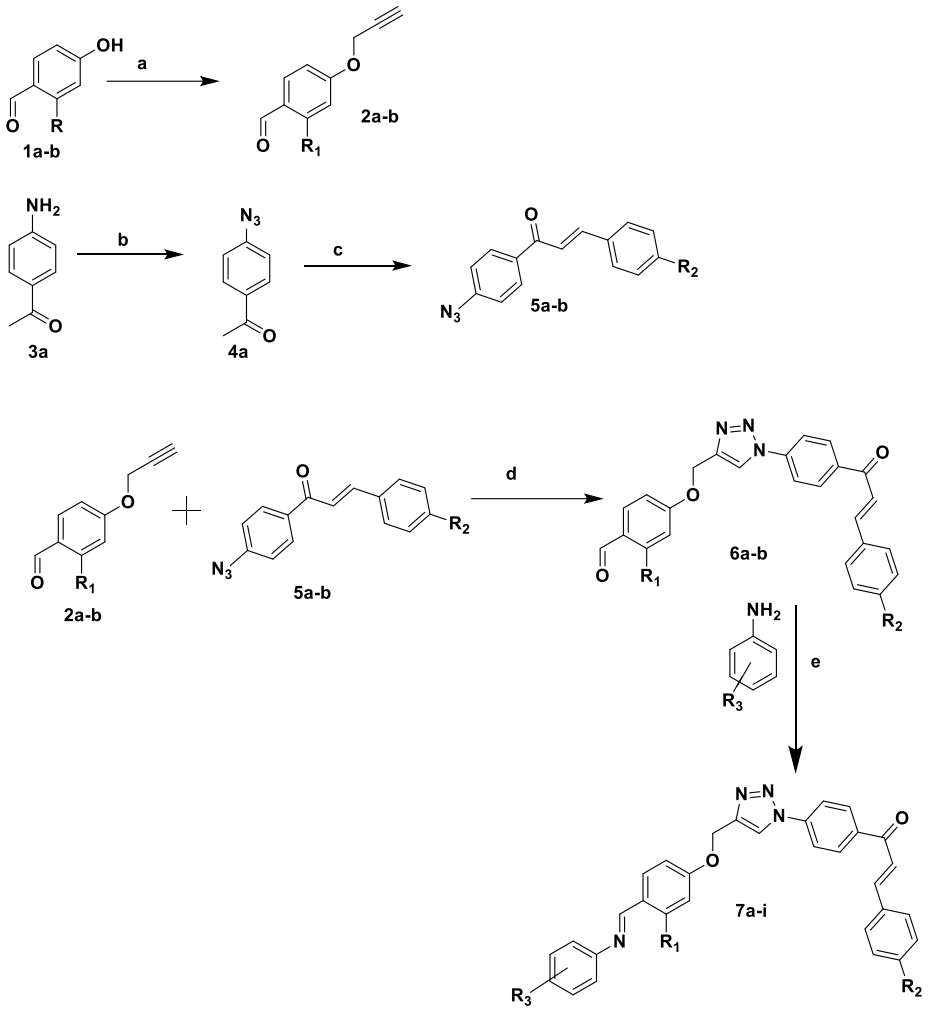
R_3 = furan-2-yl, 5-nitro-furan-2-yl, 5-(4-chlorophenyl)-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, thiophen-2-yl, 5-nitro-thiophen-2-yl, 5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl.

Scheme 2: Synthetic strategy for **dioxothiazolidin containing benzamide** derivatives.

Reagents and Conditions: a) EtOH, Conc. H_2SO_4, reflux, 12h. b) NH_2NH_2. H_2O, EtOH, reflux, 6h. c) EtOH, KOH, CS_2, reflux, 6h d) acetic anhydride, Conc. HNO_3-H_2SO_4, CH_3COONa, Pyridine 0-2°C, O/N. e) Substituted anilines, Conc. HCl, H_2O, $NaNO_2$, $CuCl_2$, 0-rt, O/N. f) acetic acid, Conc. HNO_3-H_2SO_4, 0-rt, 10h. g) Water bath heating, 2h. h) DMF, $POCl_3$, reflux, 6h. i) Acetic acid, monochloroacetic acid, acetic anhydride, sodium acetate, reflux, 10h.

Chapter 4: Synthesis and biological evalution of Schiff bases of 1,2,3-triazole derivatives

Synthetic strategy for target molecules **7a-i** is shown in **Scheme 3**. Synthesis of propynloxy benzene derivatives (**2a-b**) was done by taking vaniline (**1a**) or 4-hydroxy benzaldehyde (**1b**) with propargyl bromide in DMF solvent and K_2CO_3 as base. Terminal azido chalcones (**5a-b**) were synthesised by diazotizing 4-amino acetophenone (**3a**) which was later subjected to Claisen-Schmidt condensation with different substituted aromatic aldehydes. Novel 1,2,3-triazole derivatives (**6a-b**) were later synthesised by mixing intermediates **2a-b** and **5a-b** with tert-butanol and water (2:1) as medium in the presence of catalytic amount of sodium ascorbate and $CuSO_4.5H_2O$. The target compounds **3-phenyl-1-(4-(4-((4-((E)-(phenylimino)methyl) phenoxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one** (**7a-i**) were synthesised by reacting **6a-b** with different substituted anilines in DMF solvent. Synthesised compounds were confirmed by elemental analysis, FT IR, LC MS, ^{1}H NMR and ^{13}C NMR and were tested for their biological activity.



Where R_1 = H, OMe

R_2= OMe, 3,4-$(OMe)_2$

R_3= H, 4-Cl, 4-NO_2, 3,5-$(Cl)_2$, 2,3-$(NO_2)_2$, 3-NO_2, 2-Me-5-NO_2

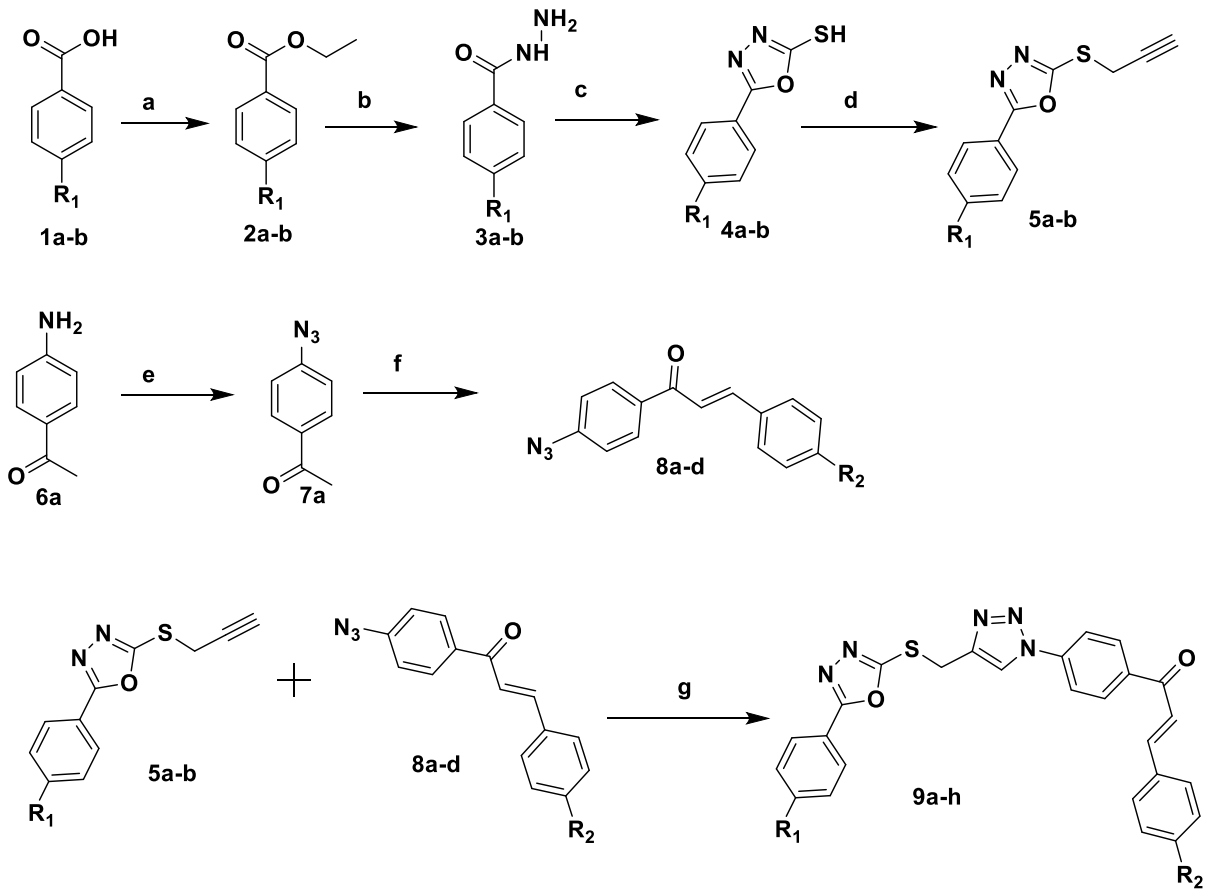
Scheme 3: Synthetic strategy for 1,2,3-triazole derivatives with schiff base.

Reagents and Conditions: a) Propargyl bromide, DMF, K_2CO_3, RT, 10h. b) Conc. HCl, H_2O, $NaNO_2$, NaN_3, 0-rt, 10h. c) substituted aromatic aldehydes, Con. H_2SO_4 , acetic acid, rt, 6-7h. d) t-BuOH- H_2O (2:1), $CuSO_4.5H_2O$, sodium ascorbate, reflux, 6-7h. e) DMF, acetic acid, reflux, 6h.

Chapter 5: Synthesis and biological evalution of 1,2,3-triazole derivatives carrying 1,3,4-oxadiazole thione.

Synthetic strategy for target molecule **9a-h** is shown in the **Scheme 4**. Substituted aromatic acids (**1a-b**) were esterified (**2a-b**) and later converted to their corresponding hydrazides (**3a-**

b). The hydrazides (**3a-b**) were converted to their corresponding oxadiazole thione derivatives (**4a-b**) in DMF medium with KOH as base. They were then treated with propargyl bromide in acetone solvent to yield terminal alkyne derivatives (**5a-b**). Terminal azido chalcones were synthesised as explained before. Target 1,2,3-triazole derivatives (**9a-h**) were synthesised in tert-butanol and water (2:1) with catalytic amount of sodium ascorbate and $CuSO_4.5H_2O$. Synthesised compounds were confirmed by elemental analysis, FT IR, LC MS, ^{1}H NMR and ^{13}C NMR and were tested for their biological activity.



Where R_1 = -Me, -OMe

R_2 = -Me, -OMe

Scheme 4: Synthetic strategy for **thiazole** derivatives.

Reagents and Conditions: a) EtOH, Con. H_2SO_4, reflux, 12h. b) NH_2NH_2. H_2O, EtOH, reflux, 6h. c) EtOH, KOH, CS_2, reflux, 6h d) Acetone, K_2CO_3, rt, 6h. e) Substituted anilines, Con HCl, H_2O, $NaNO_2$, NaN_3, 0-rt, O/N. f) acetic acid, Con H_2SO_4, rt, O/N. g) t-BuOH- H_2O (2:1), $CuSO_4.5H_2O$, sodium ascorbate, reflux, 6-7h.

Cycloaddition Approach for the Synthesis of Novel Bioactive Compounds

References

1. Arora, P., Arora, V., Lamba, H.S. and Wadhwa, D., 2012. Importance of heterocyclic chemistry: a review. *International Journal of Pharmaceutical Sciences and Research*, *3*(9), p.2947.
2. Aldwıb, A.E.O., 2021. Bazı piridin türevi 1, 3, 4-tiyadiazol bileşiklerinin eldesi ve mikrobiyolojik özelliklerinin incelenmesi (Doctoral dissertation, Kastamonu üniversitesi).
3. Al-Mulla, A., 2017. A review: biological importance of heterocyclic compounds. *Der Pharma Chemica*, *9*(13), pp.141-147.
4. Al-Mulla, A., 2017. A review: biological importance of heterocyclic compounds. Der Pharma Chemica, 9(13), pp.141-147.
5. Saleh, S.S., AL-Salihi, S.S. and Mohammed, I.A., 2019. Biological activity study for some heterocyclic compounds and their impact on the gram positive and negative bacteria. Energy Procedia, 157, pp.296-306.
6. SAGER, A.G., 2020. Microwave Synthesis and Characterization of Some Novel γ-Lactams which are Studied to Antioxidant and Biological Activity. International Journal of Pharmaceutical Research, 12(2).
7. Siddiqui, N.J., Wasake, C. and Idrees, M., 2017. Synthesis, antimicrobial, and antioxidant activities of some novel flavones and pyrazolines derived from chalcones. *Ind. J. Adv. Chem. Sci*, *5*(1), pp.43-47.
8. Gummidi, L., Kerru, N., Ebenezer, O., Awolade, P., Sanni, O., Islam, M.S. and Singh, P., 2021. Multicomponent reaction for the synthesis of new 1, 3, 4-thiadiazole-thiazolidine-4-one molecular hybrids as promising antidiabetic agents through α-glucosidase and α-amylase inhibition. *Bioorganic Chemistry*, *115*, p.105210.
9. Zhang, Z. and Yu, B., 2003. Total synthesis of the antiallergic naphtho-α-pyrone tetraglucoside, cassiaside C2, isolated from Cassia seeds. *The Journal of Organic Chemistry*, *68*(16), pp.6309-6313.
10. Crisan, L., Borota, A., Funar-Timofei, S. and Bora, A., 2020. Identification of less harmful pesticides against honey bees: shape-based similarity analysis. *Chemistry Proceedings*, *3*(1), p.22.
11. Crisan, L., Funar-Timofei, S. and Borota, A., 2022. Homology Modeling and Molecular Docking Approaches for the Proposal of Novel Insecticides against the African Malaria Mosquito (Anopheles gambiae). *Molecules*, *27*(12), p.3846.

12. Liu, Y., Qing, L., Meng, C., Shi, J., Yang, Y., Wang, Z., Han, G., Wang, Y., Ding, J., Meng, L.H. and Wang, Q., 2017. 6-OH-Phenanthroquinolizidine alkaloid and its derivatives exert potent anticancer activity by delaying S phase progression. *Journal of medicinal chemistry*, *60*(7), pp.2764-2779.
13. Agalave, S.G., Maujan, S.R. and Pore, V.S., 2011. Click chemistry: 1, 2, 3-triazoles as pharmacophores. Chemistry–An Asian Journal, 6(10), pp.2696-2718.
14. Soltis, M.J., Yeh, H.J., Cole, K.A., Whittaker, N., Wersto, R.P. and Kohn, E.C., 1996. Identification and characterization of human metabolites of CAI [5-amino-1-1 (4'-chlorobenzoyl-3, 5-dichlorobenzyl)-1, 2, 3-triazole-4-carboxamide. Drug metabolism and disposition, 24(7), pp.799-806.
15. Kohn, E.C., Reed, E., Sarosy, G.A., Minasian, L., Bauer, K.S., Bostick-Bruton, F., Kulpa, V., Fuse, E., Tompkins, A., Noone, M. and Goldspiel, B., 2001. A phase I trial of carboxyamido-triazole and paclitaxel for relapsed solid tumors: potential efficacy of the combination and demonstration of pharmacokinetic interaction. Clinical cancer research, 7(6), pp.1600-1609.
16. Fray, M.J., Bull, D.J., Carr, C.L., Gautier, E.C., Mowbray, C.E. and Stobie, A., 2001. Structure− activity relationships of 1, 4-dihydro-(1H, 4H)-quinoxaline-2, 3-diones as N-methyl-d-aspartate (glycine site) receptor antagonists. 1. Heterocyclic substituted 5-alkyl derivatives. *Journal of medicinal chemistry*, *44*(12), pp.1951-1962.
17. Pagliai, F., Pirali, T., Del Grosso, E., Di Brisco, R., Tron, G.C., Sorba, G. and Genazzani, A.A., 2006. Rapid synthesis of triazole-modified resveratrol analogues via click chemistry. *Journal of medicinal chemistry*, *49*(2), pp.467-470.
18. Aher, N.G., Pore, V.S., Mishra, N.N., Kumar, A., Shukla, P.K., Sharma, A. and Bhat, M.K., 2009. Synthesis and antifungal activity of 1, 2, 3-triazole containing fluconazole analogues. *Bioorganic & medicinal chemistry letters*, *19*(3), pp.759-763.
19. Zhang, S., Xu, Z., Gao, C., Ren, Q.C., Chang, L., Lv, Z.S. and Feng, L.S., 2017. Triazole derivatives and their anti-tubercular activity. *European journal of medicinal chemistry*, *138*, pp.501-513.
20. P Tripathi, R., S Bisht, S., Ajay, A., Sharma, A. and Misra, M., 2012. Developments in chemical approaches to treat tuberculosis in the last decade. *Current medicinal chemistry*, *19*(4), pp.488-517.
21. Singh, A., Kalamuddin, M.D., Mohmmed, A., Malhotra, P. and Hoda, N., 2019. Quinoline-triazole hybrids inhibit falcipain-2 and arrest the development of Plasmodium falciparum at the trophozoite stage. *RSC advances*, *9*(67), pp.39410-39421.

22. Costa, M.S., Boechat, N., Rangel, E.A., Da Silva, F.D.C., De Souza, A.M., Rodrigues, C.R., Castro, H.C., Junior, I.N., Lourenço, M.C.S., Wardell, S.M. and Ferreira, V.F., 2006. Synthesis, tuberculosis inhibitory activity, and SAR study of N-substituted-phenyl-1, 2, 3-triazole derivatives. Bioorganic & medicinal chemistry, 14(24), pp.8644-8653.
23. Dabak, K., Sezer, Ö., Akar, A. and Anaç, O., 2003. Synthesis and investigation of tuberculosis inhibition activities of some 1, 2, 3-triazole derivatives. European journal of medicinal chemistry, 38(2), pp.215-218.
24. Yadav, P., Lal, K., Kumar, L., Kumar, A., Kumar, A., Paul, A.K. and Kumar, R., 2018. Synthesis, crystal structure and antimicrobial potential of some fluorinated chalcone-1, 2, 3-triazole conjugates. European journal of medicinal chemistry, 155, pp.263-274.
25. Shyma, P.C., Kalluraya, B., Peethambar, S.K. and Vijesh, A.M., 2016. Regioselective one pot synthesis of 1, 2, 3-triazole derivatives bearing phthalazine moiety and their pharmacological activity. Medicinal Chemistry Research, 25(11), pp.2680-2690.
26. Padwa, A. ed., 1984. 1, 3-Dipolar cycloaddition chemistry. Wiley-interscience.
27. Huisgen, R., 1963. 1.3-Dipolare Cycloadditionen Rückschau und Ausblick. Angewandte Chemie, 75(13), pp.604-637.
28. Küçükoğlu, K., Acar Çevik, U., Nadaroglu, H., Celik, I., Işık, A., Bostancı, H.E., Özkay, Y. and Kaplancıklı, Z.A., 2022. Design, synthesis and molecular docking studies of novel benzimidazole-1, 3, 4-oxadiazole hybrids for their carbonic anhydrase inhibitory and antioxidant effects. Medicinal Chemistry Research, 31(10), pp.1771-1782.
29. Salahuddin, Mazumder, A., Yar, M.S., Mazumder, R., Chakraborthy, G.S., Ahsan, M.J. and Rahman, M.U., 2017. Updates on synthesis and biological activities of 1, 3, 4-oxadiazole: A review. Synthetic Communications, 47(20), pp.1805-1847.
30. Joule, J.A., Mills, K. and Smith, G.F., 2020. Heterocyclic chemistry. CRC Press.
31. Sahoo BM, Kumar RBVV and Kumari BUBP: Synthesis, characterisation and biological evaluation of novel oxadiazole derivatives. International Journal of Pharmaceutical Sciences and Research 2011; 2(2): 344-50.
32. Godhani, D.R., Mulani, V.B. and Mehta, J.P., 2019. Cyclization and antimicrobial evolution of 1, 3, 4-oxadiazoles by carbohydrazide. World Scientific News, 124(2), pp.304-311.
33. Godhani DR, Mulani VB, Mehta JP. Cyclization and antimicrobial evolution of 1, 3, 4-oxadiazoles by carbohydrazide. World Scientific News. 2019;124(2):304-11.
34. Polothi, R., Raolji, G.S.B., Kuchibhotla, V.S., Sheelam, K., Tuniki, B. and Thodupunuri, P., 2019. Synthesis and biological evaluation of 1, 2, 4-oxadiazole linked 1, 3, 4-oxadiazole derivatives as tubulin binding agents. Synthetic Communications, 49(13), pp.1603-1612.

35. Shridhar, A.H., Keshavayya, J., Peethambar, S.K. and Hoskeri, H.J., 2016. Synthesis and biological activities of Bis alkyl 1, 3, 4-oxadiazole incorporated azo dye derivatives. Arabian Journal of Chemistry, 9, pp.S1643-S1648.
36. Khalilullah, H., Khan, S., Nomani, M.S. and Ahmed, B., 2016. Synthesis, characterization and antimicrobial activity of benzodioxane ring containing 1, 3, 4-oxadiazole derivatives. Arabian Journal of Chemistry, 9, pp.S1029-S1035.
37. Mohan, T.P., Vishalakshi, B., Bhat, K.S., Rao, K.S. and Kendappa, G.N., 2004. Synthesis and insecticidal activity of some 1, 3, 4-oxadiazole derivatives containing phenoxyfluorophenyl group.
38. Wang, B.L., Zhu, H.W., Ma, Y., Xiong, L.X., Li, Y.Q., Zhao, Y., Zhang, J.F., Chen, Y.W., Zhou, S. and Li, Z.M., 2013. Synthesis, insecticidal activities, and SAR studies of novel pyridylpyrazole acid derivatives based on amide bridge modification of anthranilic diamide insecticides. Journal of agricultural and food chemistry, 61(23), pp.5483-5493.
39. Bankar, G.R., Nandakumar, K., Nayak, P.G., Thakur, A., Chamallamudi, M.R. and Nampurath, G.K., 2009. Vasorelaxant effect in rat aortic rings through calcium channel blockage: A preliminary in vitro assessment of a 1, 3, 4-oxadiazole derivative. Chemico-Biological Interactions, 181(3), pp.377-382.
40. Bankar, G.R., Nampurath, G.K., Nayak, P.G. and Bhattacharya, S., 2010. A possible correlation between the correction of endothelial dysfunction and normalization of high blood pressure levels by 1, 3, 4-oxadiazole derivative, an L-type Ca2+ channel blocker in deoxycorticosterone acetate and NG-nitro-l-arginine hypertensive rats. Chemico-biological interactions, 183(2), pp.327-331.
41. Tabatabai, S.A., Lashkari, S.B., Zarrindast, M.R., Gholibeikian, M. and Shafiee, A., 2013. Design, synthesis and anticonvulsant activity of 2-(2-phenoxy) phenyl-1, 3, 4-oxadiazole derivatives. Iranian Journal of Pharmaceutical Research: IJPR, 12(Suppl), p.105.
42. P Harish, K., N Mohana, K., Mallesha, L., Veeresh, B., Madhava Reddy, B. and Kumar, N.N., 2013. Synthesis and Evaluation of In Vivo Anticonvulsant Activity of 2, 5-Disubstituted-1, 3, 4-Oxadiazole Derivatives. Letters in Drug Design & Discovery, 10(8), pp.783-791.
43. W.B. Stillman, A.B. Scott, J.M.Clampit, U.S.Pat., 2, 319, 481 (1943); Chem. Abstr., 37, 6413 (1943)
44. Dann, O. and Möller, E.F., 1947. Bakteriostatisch wirkende Nitro-Verbindungen des Thiophens und Furans. Chemische Berichte, 80(1), pp.23-36.

45. Dodd, M.C., Stillman, W.B., Roys, M. and Crosby, C., 1944. The in vitro bacteriostatic action of some simple furan derivatives. Journal of pharmacology and experimental therapeutics, 82(1), pp.11-18.
46. Pires, J.R., Saito, C., Gomes, S.L., Giesbrecht, A.M. and Amaral, A.T.D., 2001. Investigation of 5-Nitrofuran Derivatives: Synthesis, Antibacterial Activity, and Quantitative Structure− Activity Relationships. Journal of medicinal chemistry, 44(22), pp.3673-3681.
47. Szarvasi, E., Fontaine, L. and Betbeder-Matibet, A., 1973. Antimicrobials. New nitrofuran derivatives. Journal of Medicinal Chemistry, 16(3), pp.281-287.
48. Michels, J.G., 1960. Chemotherapeutic Nitrofurans. VI. 3-(5-Nitrofurfurylideneamino) tetrahydro-2 (1H) pyrimidinone. The Journal of Organic Chemistry, 25(12), pp.2246-2247.
49. Hulbert, P.B., Bueding, E. and Robinson, C.H., 1973. Structure and antischistosomal activity in the nitrofuran series. Requirement for a 5-nitro-2-furyl-vinyl moiety based on comparison of 3-(5-nitro-2-furyl)-substituted propionic, acrylic, and propiolic acid derivatives. Journal of Medicinal Chemistry, 16(1), pp.72-78.
50. Kempf, D.J.; Sham, H.L.; Marsh, K.C.; Flentge, C.A.; Betebenner, D.; Green, B.E.; McDonald, E.; Vasavanonda, S.; Saldivar, A.; Wideburg, N.E.; Kati, W.M. J. Med. Chem. 1998, 41(4), 602-617.
51. Mena-Rejon, G.; Perez-Navarro, Y.; Torres-Romero, J.C.; Vazquez-Carrillo, L.; Carballo, R.M.; Arreola, R.; Herrera-Espana, A.; Arana-Argaez, V.; Quijano-Quinones, R.; Fernandez-Sanchez, J.M.; Alvarez-Sanchez, M.E. *Parasitol. Res.* 2021, *120*(1), 233-241.
52. Bian, Q.; Zhao, R.Q.; Peng, X.J.; Gao, L.J.; Zhou, G.N.; Yu, S.J.; Zhao, W.G. Design, *J. Agri. Food Chem.* 2021, *69*, 3848-3858.
53. El-Naggar, A.M.; El-Hashash, M.A.; Elkaeed, E.B. *Bioorg. Chem.* **2021**, *108*, 104615.
54. 19. Shetty, N.S.; Khazi, I.A.M.; Ahn, C.J. *Bull. Korean Chem. Soc.* **2010**, *31*(8), 2337-2340.
55. 20. Syed, M.A.; Yiragamreddy, P.R.; Chandrasekhar, K.B. *Ind. J. Het. Chem.* **2017**, *27*, 329-338.
56. .a) Sultana, F.; Bonam, S.R.; Reddy, V.G.; Nayak, V.L.; Akunuri, R.; Routhu, S.R.; Alarifi, A.; Halmuthur, M.S.K.; Kamal, A. *Bioorg. Chem.* **2018**, *76*, 1-12.
b) Shaik, S.P.; Nayak, V.L.; Sultana, F.; Rao, A.S.; Shaik, A.B.; Babu, K.S.; Kamal, A. *Eur. J. Med. Chem.* **2017**, *126*, 36-51.
c) Baig, M.F.; Nayak, V.L.; Budaganaboyina, P.; Mullagiri, K.; Sunkari, S.; Gour, J.;

57. Kamal, A. *Bioorg. Chem.* **2018**, *77*, 515-526.

58. Dincel, E.D.; Gursoy, E.; Yilmaz-Ozden, T.; Ulusoy-Guzeldemirci, N. *Bioorg. Chem.* **2020**, *103*, 104220.

59. Schiff, H., 1864. Mittheilungen aus dem Universitätslaboratorium in Pisa: eine neue Reihe organischer Basen. Justus Liebigs Annalen der Chemie, 131(1), pp.118-119.

60. Souza, A.O.D., Galetti, F., Silva, C.L., Bicalho, B., Parma, M.M., Fonseca, S.F., Marsaioli, A.J., Trindade, A.C., Gil, R.P.F., Bezerra, F.S. and Andrade-Neto, M., 2007. Antimycobacterial and cytotoxicity activity of synthetic and natural compounds. Química Nova, 30, pp.1563-1566.

61. Shi, L., Ge, H.M., Tan, S.H., Li, H.Q., Song, Y.C., Zhu, H.L. and Tan, R.X., 2007. Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde. European journal of medicinal chemistry, 42(4), pp.558-564.

62. Rehman, W., Baloch, M.K., Muhammad, B., Badshah, A. and Khan, K.M., 2004. Characteristic spectral studies andin vitro antifungal activity of some Schiff bases and their organotin (IV) complexes. Chinese Science Bulletin, 49(2), pp.119-122.

63. Wang, P.H., Keck, J.G., Lien, E.J. and Lai, M.M., 1990. Design, synthesis, testing, and quantitative structure-activity relationship analysis of substituted salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus. Journal of medicinal chemistry, 33(2), pp.608-614.

64. Sriram, D., Yogeeswari, P., Myneedu, N.S. and Saraswat, V., 2006. Abacavir prodrugs: microwave-assisted synthesis and their evaluation of anti-HIV activities. Bioorganic & medicinal chemistry letters, 16(8), pp.2127-2129.

List of Publications

Journal Publications

1. **Tharangini K. Shreekanth**., Hemmige S. Yathirajan, Balakrishna Kalluraya, Sabine Foro, and Christopher Glidewell. "Order versus disorder in two isomorphous pyrazolone-substituted diethyl propanedioates prepared using a three-component one-pot reaction under solvent-free conditions." Acta Crystallographica Section E: Crystallographic Communications 76, no. 10 (2020): 1605-1610.
2. Nagaraja, Manju, Balakrishna Kalluraya, **Tharangini K. Shreekanth**, and Madan S. Kumar. "Synthesis of chalcone precursor via Cu (I) catalyzed 1, 3-dipolar reaction of functionalized

acetylene and pyrazole embedded dipole." *Journal of Heterocyclic Chemistry* 57, no. 10 (2020): 3642-3652.

Conference Presentations

1. **Tharangini K S** and Balakrishna Kalluraya, Synthesis and SAR studies of some novel series of pyrimidine analogues, 39th Annual national conference of Indian Council of Chemists, held by Veera Narmada South Gujrat University, Gujrat on 11th April 2021 in virtual mode.
2. **Tharangini K S** and Balakrishna Kalluraya, Kelavu hosabageya sarani pyrimidine sadrushyagala samshleshane matthu avugala rachane matthu chatuvatikegalige sambandhisida adhyana" in 16th Kannada-Vijnana Sammelana held at Mangalore University, Mangalagangotri on 15-17 th September 2021 awarded with Athyuttama Mahila Prashasthi.
3. **Tharangini K S** and Balakrishna Kalluraya, Discovery of novel bioactive thiazolo oxadiazole derivatives, National conference on "Impact of Chemistry and Biology to the Society and Industry", ICBSI-2022 on May 20th and 21st at Kuvempu University, Shivamogga.
4. **Tharangini K S** and Balakrishna Kalluraya, Synthesis and evaluation of antioxidant properties of novel 7a-hydroxy-7ah-Thiazolo[2,3-b][1,3,4]oxadiazol-5(6h)-one derivatives, National conference on "New Vistas In Chemistry", on August 3rd-4th at Jnanabharathi Campus, Bangalore University.

Miss. Tharangini K S
Research Scholar

Prof. Balakrishna Kalluraya
Research Guide